DOI:
10.1038/s41390-019-0619-x

Document Version
Peer reviewed version

Electrical activity of the diaphragm following a loading dose of caffeine citrate in ventilated preterm infants

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Running title: Caffeine and diaphragm EMG activity

Author Contributions: AG and KAH designed the study, EEW, KAH, JJ and RS-R collected the data, EEW, TD and AG analysed the data and produced the first draft. All authors were involved in revising it critically for important intellectual content and gave final approval of the version to be published.

Statement of Financial support: The research was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Financial disclosure: The authors have no financial relationships relevant to this article to disclose. The EMG equipment was provided by SLE.

Conflict of interest: Professor Greenough has a non-conditional educational grant from SLE to support her research on optimising neonatal ventilation.

Category of study: Clinical

What is the key message of your article?

- Intravenous administration of caffeine citrate in ventilated, prematurely born neonates transiently increased the diaphragmatic EMG activity and improved respiratory function.

What does it add to the existing literature?

- This is the first study to assess the impact of caffeine on the diaphragmatic EMG activity in ventilated neonates.

What is the impact?

- Our results describe a mechanism by which caffeine administration might facilitate extubation of ventilated, prematurely born infants.

ABSTRACT

Background: Administration of caffeine citrate can facilitate extubation. Our aim was to determine whether a loading dose of caffeine citrate given to ventilated, preterm infants affected the diaphragm electrical activity.

Methods: Infants < 34 weeks of gestational age were recruited if requiring mechanical ventilation and prescribed a loading dose of caffeine citrate. Surface electrodes recorded the electrical activity of the diaphragm (dEMG) before and after administration of intravenous caffeine citrate. The mean amplitude of the EMG (dEMG) trace and the mean area under the EMG curve (aEMGc) were calculated.

Results: Thirty-two infants were assessed with a median gestational age of 29 (27 to 31) weeks. The dEMG amplitude increased, peaking at 25 minutes post administration (p=0.006) and the increase in aEMGc (p= 0.004) peaked at 30 minutes, the differences were not significant after 60 minutes. At 20 minutes there was an increase in minute volume (p= 0.034) and a reduction in the peak inspiratory pressure (p= 0.049).

Conclusion: We have demonstrated a transient increase in both electrical activity of the diaphragm and respiratory function following an intravenous loading dose of caffeine citrate.

INTRODUCTION

Mechanical ventilation is frequently used to support very prematurely born infants who have immature, underdeveloped lungs and inadequate respiratory drive. Yet, prolonged ventilation is associated with complications such as bronchopulmonary dysplasia and pulmonary interstitial emphysema (1, 2) and hence, it is important to successfully extubate infants as soon as possible. Caffeine citrate is a methylxanthine and administration can facilitate successful extubation through a number of mechanisms (3). Caffeine citrate is a respiratory stimulant that acts centrally and antagonises inhibitory adenosine A_1 receptors (4). It increases the ventilatory response to hypercapnia in preterm infants (5). Furthermore, administration of caffeine citrate can increase respiratory muscle strength and improve lung compliance (6). Intravenous caffeine citrate has also been shown to increase the diaphragmatic activity of spontaneously breathing preterm infants with a corresponding increase in tidal volume (7). Whether, however the effects of caffeine citrate administration on diaphragm electrical activity are similar in ventilated, preterm infants is currently unknown.

Electromyography (EMG) is a global measure of the neural impulses that are translated into muscle fibre action potentials, with the processed signal giving the amplitude of electrical activity of a muscle (8). The amplitude of the electrical activity of the diaphragm (EAdi) is helpful in monitoring asynchrony and respiratory muscle loading of ventilated patients (8). The electrical activity of the diaphragm can also be used to assess neural respiratory drive (9, 10); inspiratory drive has been shown to increase in response to an increased work of breathing (11). We hypothesised that administration of a loading dose of caffeine citrate to ventilated, prematurely born infants would result in an increase in the amplitude of the

diaphragm electromyogram and improved respiratory function. Our aim was to test those hypotheses.

METHODS

Study design and subjects

A prospective, observational cohort study took place between 01/09/2018 and 30/06/2019 at the two neonatal units within King's College Hospital NHS Foundation Trust (KCH), London UK. This NHS Foundation Trust comprises of King's College Hospital, London and the Princess Royal University Hospital, Orpington. The London Brent Research Ethics Committee approved the study and the parents gave written, informed consent for their infant to take part.

Infants born less than 34 weeks of completed gestational age who were prescribed a loading dose of caffeine citrate by the clinical team were eligible for recruitment into the study if they were receiving invasive mechanical ventilation. Infants with chromosomal or major congenital anomalies were excluded. Baseline demographic data were collected including gender, ethnicity, antenatal exposure to corticosteroids and magnesium sulphate, gestational age and mode of delivery, mode of ventilation prior to caffeine administration and use of postnatal surfactant.

At KCH, ventilatory support was delivered by an SLE 6000 ventilator (SLE limited, Croydon UK). Preterm infants were usually supported by patient triggered ventilation (PTV) with a targeted tidal volume. Targeted-tidal volumes were set between 5-6 mL/kg. The clinical team routinely prescribed a 20-minute loading dose caffeine citrate (20mg/kg) to ventilated infants less than 34 weeks of gestational age as per Trust guidelines and in agreement with recent evidence showing the benefit of early therapy (before day three of postnatal life) in decreasing the composite outcome of BPD or all-cause mortality (12).

Diaphragmatic electrical activity was measured continuously 15 minutes prior to the administration of a loading dose of caffeine citrate and until 180 minutes after the loading dose. The peak inspiratory pressure, positive end expiratory pressure, expired tidal volume, fraction of inspired oxygen, inspiratory time and mean airway pressure were recorded during the same time periods as the EMG analysis.

The activity of the diaphragm was measured via transcutaneous electromyography (EMG) of the diaphragm using surface electrodes. All infants were assessed in the supine position. The transcutaneous diaphragm EMG was monitored using a portable 16-channel digital physiological amplifier (Dipha-16; Inbiolab, Groningen, the Netherlands) and three surface electrodes (Kendall H59P cloth electrodes; Covidien, Massachusetts). Two electrodes were placed vertically in line with the nipples on the right and left chest wall at the costo-abdominal margin and one electrode placed at the centre of the sternum. The electrodes were connected to a portable physiological amplifier (DEMCON; Macawi Medical Systems, the Netherlands) that generated raw signals correlating to the diaphragm EMG at a sampling rate of 500Hz. The physiological amplifier wirelessly transmitted to a bedside computer running Polybench (Applied Biosignals, Weener, Germany). Raw signals were filtered and processed automatically within the Polybench software including the gating technique. The method used to filter the cardiac electrical activity was similar to the gating technique described by O'Brien (13). EMG data were imported into MATLAB from Poly5 format using the TMSi MATLAB Interface (Twente Medical Systems International, Oldenzaal, the Netherlands). The complete recording of each infant was reviewed and points at which the infants was moving or being handled were identified by the presence of interference to the signal, these were excluded from analysis. EMG analyses of periods of 30-second artefact free recordings were performed at set time intervals. Three sets of stable 30-second recordings in a time

period beginning five minutes prior to administration of the loading dose of caffeine citrate and at 5, 20, 25, 30, 60, 120 and 180-minute time intervals after the start of the 20-minute caffeine citrate loading dose infusion were analysed. For each artefact free 30-second recording, the mean amplitude of the EMG (dEMG) trace and the mean area under the EMG curve (aEMGc) (14, 15) were calculated using MATLAB Statistics Toolbox Release 2015b (The MathWorks, Inc., Natick, MA, USA). At each time interval, the change from the baseline for each measurement was calculated with each infant acting as their own control.

Analysis

The data were tested for normality using the Shapiro-Wilk test and found to be non-normally distributed. Therefore, data are presented as median (IQR) and differences assessed for statistical significance using the Wilcoxon rank sum test for paired changes post caffeine administration. Statistical analyses were undertaken using SPSS software Version 25 (SPSS Inc., Chicago IL).

Sample Size

A previous study found an increase in median peak electrical activity from 1.42μV to 2.16μV in non-ventilated infants following caffeine administration (7), therefore, using an estimated sample mean of 1.4μV ± 0.6μV, to detect a 30% difference in peak diaphragm EMG with 80% power at the 5% significance level a sample of 32 infants was recruited.

RESULTS

During the study period, 110 infants born less than 34 weeks of completed gestational age were admitted to the neonatal unit, 32 were recruited (Figure 1) (Table 1). There were no significant differences in gestational age (GA) and birthweight (BW) between the included

infants and those 15 infants who were eligible but not included (GA: 31.14 (25.0-32.71) weeks, p=0.817; BW: 1.15 (0.73-1.91) kg, p=0.71). In the included infants, the median time after birth to caffeine citrate administration was 288 (133-745) minutes (Table 1).

There was a significant increase in dEMG amplitude from baseline following the loading dose of caffeine citrate that peaked at 25 minutes post administration (p=0.006), and a significant increase in aEMGc from baseline peaking at 30 minutes post administration of caffeine citrate (p=0.004). By 60 minutes the loading dose of caffeine citrate had no significant effect on the electrical activity of the diaphragm (Figures 2 and 3). At 20 minutes there was a significant increase in minute volume (p=0.034) from baseline and significant reduction from baseline in the peak inspiratory pressure (p=0.049) and at 30 minutes a significant increase in the respiratory rate (p=0.021) from baseline. There were no significant changes in tidal volume post caffeine administration (Table 2).

DISCUSSION

We have demonstrated that in preterm, ventilated infants there was a significant increase in both the dEMG amplitude and aEMGc, which peaked within the first hour following a loading dose of caffeine citrate. This transient increase in diaphragmatic electrical activity post administration of intravenous caffeine citrate is in agreement with a recent study in non-ventilated newborns (7). It may be explained by the initial high peak serum levels seen

shortly after administration of the loading dose of caffeine. The timing of the increase in diaphragmatic activity was associated with improvements in lung function as shown by the increase in minute volume and decrease in peak inspiratory pressure.

The current study measured electrical activity and not contractions of the diaphragm. One in vivo study found, however, that administration of theophylline resulted in an increase in minute ventilation, which correlated with an increase in diaphragmatic contractility as well as inspiratory diaphragmatic neuromuscular output (16). What is unknown, however, is the underlying mechanism by which caffeine acts to enhance this contractile nature. One adult study showed an increase in trans-diaphragmatic pressure post caffeine therapy implying that caffeine does indeed enhance muscle contractility of the diaphragm (17). It has been suggested that caffeine acts centrally by rapidly crossing the blood brain barrier (18) and through transmission of neural impulses has subsequent effects on respiratory function resulting in increased diaphragmatic muscle activity (19). A further possibility is that caffeine increases sarcoplasmic reticulum calcium concentrations (17, 20) and hence enhances the activation of contractile proteins by increasing the affinity of calcium activation sites for calcium ions (21).

A previous study described a significant increase in tidal volume post caffeine citrate administration in non-invasively ventilated infants, which was shown to correlate with the increase in dEMG amplitude (7). The majority of infants in the present study were supported with a predetermined targeted tidal volume, hence we would not have expected to see a change in the expiratory tidal volume. As lung mechanics change over time, the peak inspiratory pressure (PIP) required to achieve a target tidal volume will change. In this study, we observed a statistically significant decrease in PIP post caffeine administration with a

corresponding increase in minute volume with an increase in respiratory rate demonstrating the increase in diaphragmatic electrical activity favourably influenced respiratory function.

The elimination half-life of caffeine citrate is 101 hours in infants (22), compared to the three to six hour half-life observed in adults (4). It has been shown, however, that there is a high variation in the elimination half-life between neonates of relatively similar conceptional ages (23). Moreover, one study showed that peak concentrations of both oral and intravenous caffeine citrate are observed at between 30 minutes to two hours following administration (24). We speculate that the physiological effects of caffeine citrate in our study peaking within the first one hour post administration are related to the time to peak effect (T_{max}) at the peak concentration (C_{max}), and not related to the maximum possible effect of the drug (E_{max}) (25).

Our study has strengths and some limitations. This study used non-invasive techniques for monitoring, with the use of surface electrodes, which were generally acceptable to parents with only two parents declining participation. There is ease and simplicity in using surface electrodes and these can be used for infants of all gestational ages (26). Diaphragm electromyogram recording by surface electrodes could potentially be susceptible to interference from surrounding muscle groups such as intercostal and abdominal. On analysis of the traces, however, little interference was seen. This is in agreement with one previous study of diaphragm electrical recordings that showed little cross talk of intercostal and abdominal muscles with diaphragmatic activity (27). Interventions such as neonatal procedures, nursing cares or position changes were not controlled for due to the acute setting and timing of the study, and these may have had some interference on the dEMG signal as movement artefacts, however this limitation was accounted for by selecting the closest 30-

second artefact free period at each time interval studied. Overall, we saw a positive response in electrical activity following caffeine administration, but the response was variable. Our sample size, unfortunately, precludes sub-group analysis. A further limitation of this study was the non-randomisation of infants, but as caffeine has been shown to be beneficial to all premature infants (28, 29) it would be unethical to randomise infants.

In conclusion, we have demonstrated that a loading dose of caffeine citrate in ventilated preterm infants had a transient increase in the electrical activity of the diaphragm and improvement in respiratory function. The transient nature of the effects we describe have implications for neonatal clinicians, that is if extubation is not soon after the loading dose of caffeine citrate has been administered, it may be less effective in facilitating extubation, but there is no evidence that this would impinge on its proven effects on improving neurodevelopmental outcome (30).

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Acknowledgments

We would like to thank Dr Ian Hunt who supported analysis of the data.

FIGURE LEGENDS

Figure 1. Consort flow diagram of recruitment process

Figure 2. Boxplot of percentage change in diaphragm amplitude over time. The ends of each box represent the upper and lower quartiles with the median being marked by a horizontal line inside the box. The whiskers are the two lines outside the box that extend to the highest and lowest observations.

Figure 3. Boxplot of percentage change in area under the EMG curve over time. The ends of each box represent the upper and lower quartiles with the median being marked by a horizontal line inside the box. The whiskers are the two lines outside the box that extend to the highest and lowest observations.

Table 1. Baseline demographics

Data are presented as median (interquartile range) or n (%)

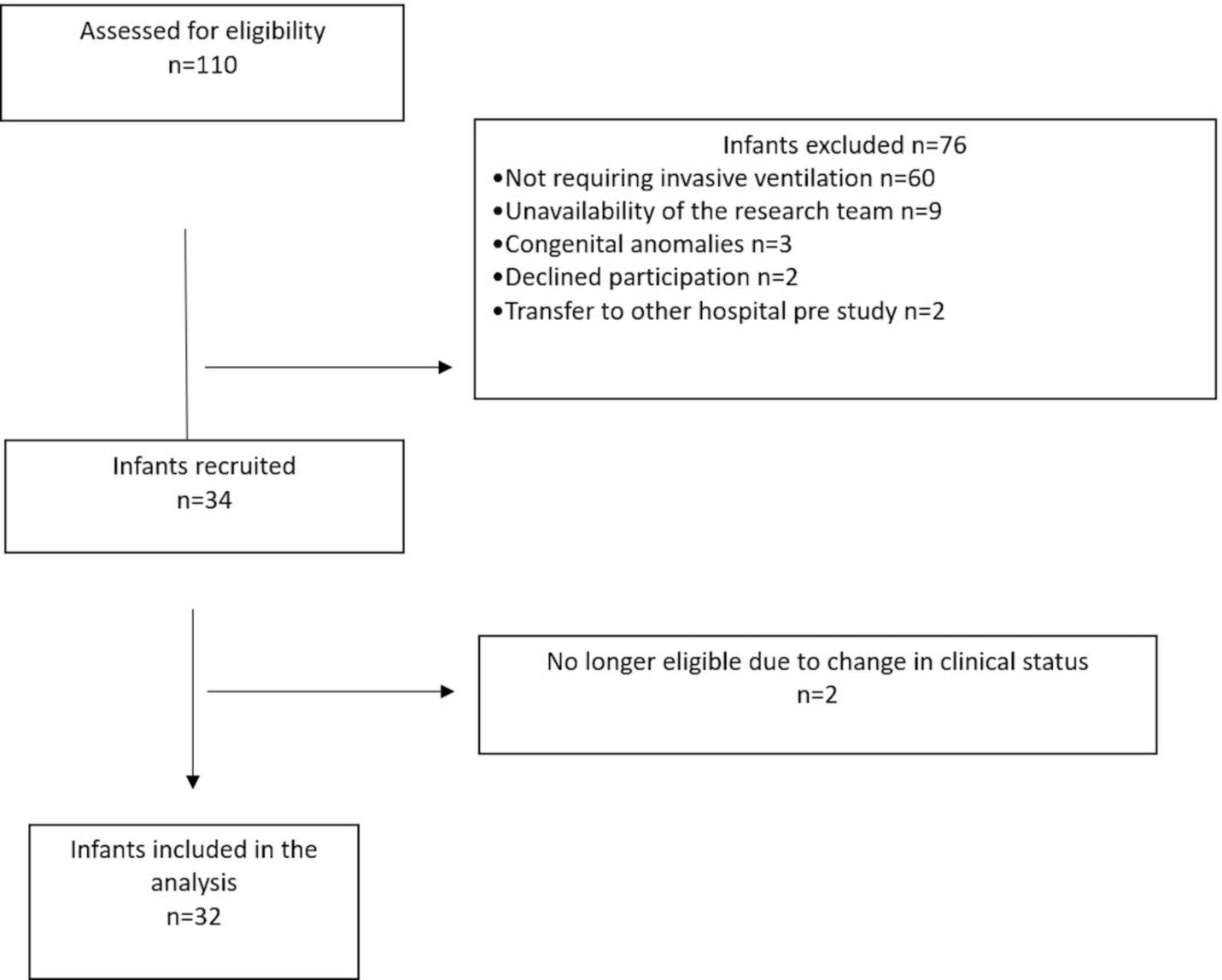
n	32
Gestational age (weeks)	29.71 (27.27-31.49)
Birthweight (kg)	1.15 (0.84-1.44)
Antenatal steroids	29 (90.6)
Male sex	13 (40.6)
Apgar Score at:	
1 min	6 (3-7)
5 mins	8 (7-9)
10 mins	9 (8.3-10)
Reason for intubation	
Increased FiO_2	4 (12.5)
Increased work of breathing	8 (25)
Poor respiratory effort	11 (34.4)
Chest x-ray changes	1 (3.1)
Apnoea	8 (25)
Where intubated	
Delivery suite	30 (93.8)
NNU	2 (6.3)
Time of delivery suite intubation post birth (mins)	6 (4.0-10.3)
Time post birth to caffeine (mins)	288 (133-746)
Postnatal surfactant	32 (100)
Mode of ventilation	
PTV	30 (93.8)
SIMV	2 (6.3)
Added TTV	28 (87.5)
FiO_2 at the time of study	0.3 (0.23-0.40)
PEEP (cmH_2O)	5.2 (5.0-5.7)

GA = gestational age; BW = birthweight, FiO_2 = fraction of inspired oxygen, PEEP = positive end expiratory pressure

Table 2. Diaphragmatic activity and respiratory function before and after a loading dose of caffeine
Data are presented as median (interquartile range)
RR = respiratory rate; MV = minute volume; TV = tidal volume; PIP = peak inspiratory pressure

	Baseline	**5 mins**	**20 mins**	**25 mins**	**30 mins**	**1 hour**	**2 hours**	**3 hours**
dEMG (µV)	1.60 (0.77-2.25)	1.72 (0.84-2.67), **p=0.015**	1.63 (0.87-2.45), p=0.217	2.01 (0.92-2.52), **p=0.006**	1.96 (0.98-2.40), **p=0.011**	1.53 (0.82-2.45), p=0.295	1.47 (0.78-2.26), p=0.517	1.43 (0.82-2.19), p=0.792
aEMGc (µV.S)	2.39 (1.58-2.66)	2.69 (2.02-3.15), **p<0.001**	2.40 (1.68-3.16), p=0.115	2.58 (1.95-3.18), **p=0.005**	2.59 (1.96-3.27), **p=0.004**	2.33 (1.74-2.96), p=0.231	2.29 (1.70-2.86), p=0.735	2.53 (1.79-2.91), p=0.360
RR (bpm)	56.0 (42.7-70.7)	56.4 (48.0-67.9), p=0.455	60.4 (53.8-79.5), p=0.152	50.5 (39.9-61.8), p=0.164	61.5 (45.0-73.6), **p=0.021**	57.5 (40.1-73.1), p=0.902	65.7 (53.4-77.9), p=0.069	60.5 (51.9-73.0), p=0.645
MV (mL/min)	377.5 (224.6-502.5)	320 (220.0-480.0), p=0.479	395.6 (282.0-528.0), **p=0.034**	405.26 (247.8-517.5), p=0.124	380.0 (227.7-500.0), p=0.163	369.9 (231.8-528.9), p=0.759	370 (247.2-530.0), p=0.469	410.0 (270.0-510.0), p=0.879
TV (mL)	6.4 (4.9-8.1)	6.1 (4.28-7.35), p=0.974	6.7 (4.98-7.63), p=0.524	6.9 (4.7-7.7), p=0.401	6.1 (4.8-7.8), p=1.0	6.25 (4.8-8.3), p=0.642	5.7 (4.53-7.33), p=-0.249	5.5 (4.1-7.8), p=0.318
PIP (cmH_2O)	16.7 (12.1-20.0)	16.8 (12.8-20.0), p=0.638	12.9 (10.3-19.8), **p=0.049**	15.3 (13.8-20.0), p=0.912	15.9 (12.1-20.0), p=0.737	16.6 (11.6-19.8), p=0.935	16.3 (11.2-20.0), p=0.470	16.1 (11.4-20.0), p=0.623

Figure 1. Consort flow diagram of recruitment process



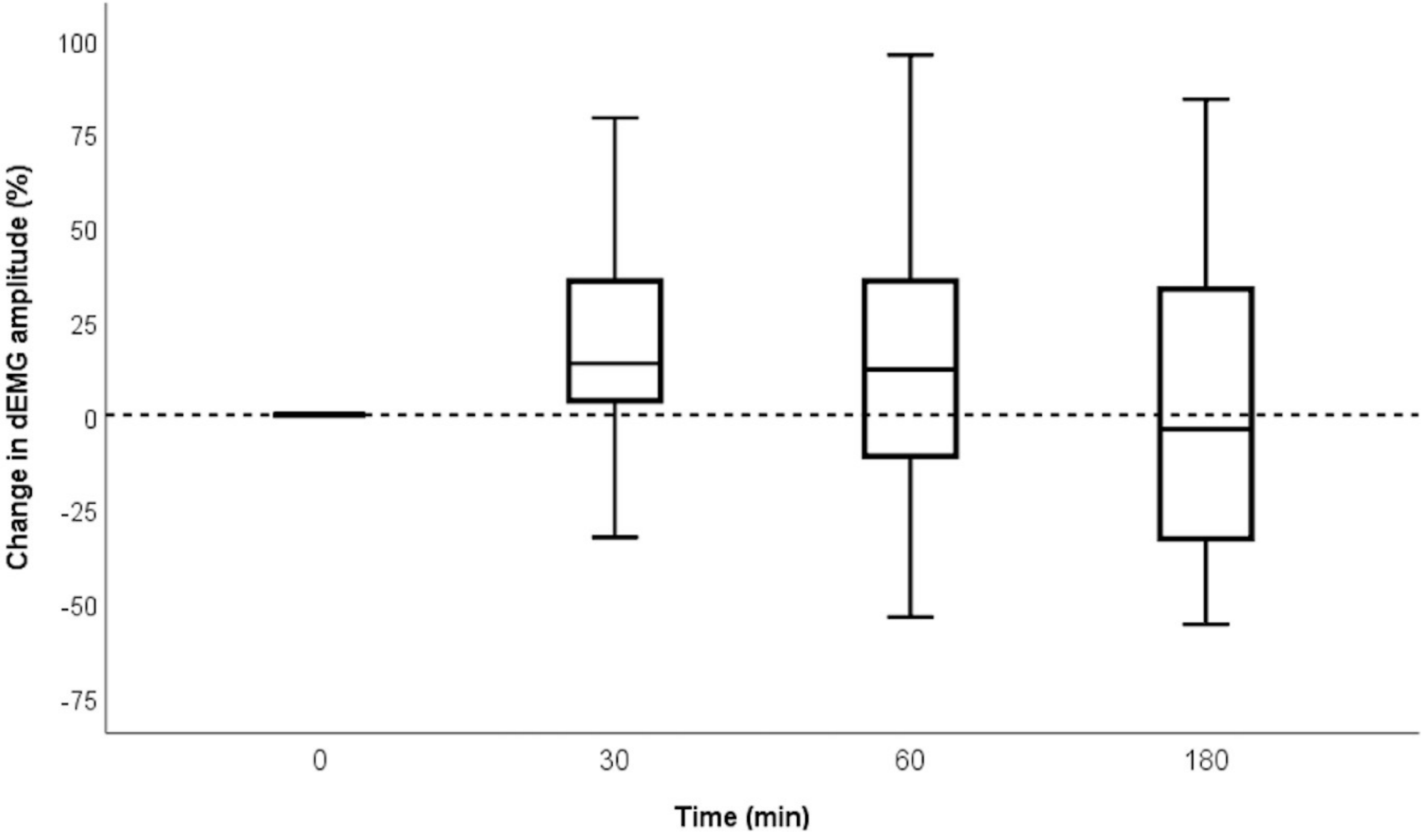


Figure 2. Boxplot of percentage change in diaphragm amplitude over time

The ends of each box represent the upper and lower quartiles with the median being marked by a horizontal line inside the box. The whiskers are the two lines outside the box that extend to the highest and lowest observations.

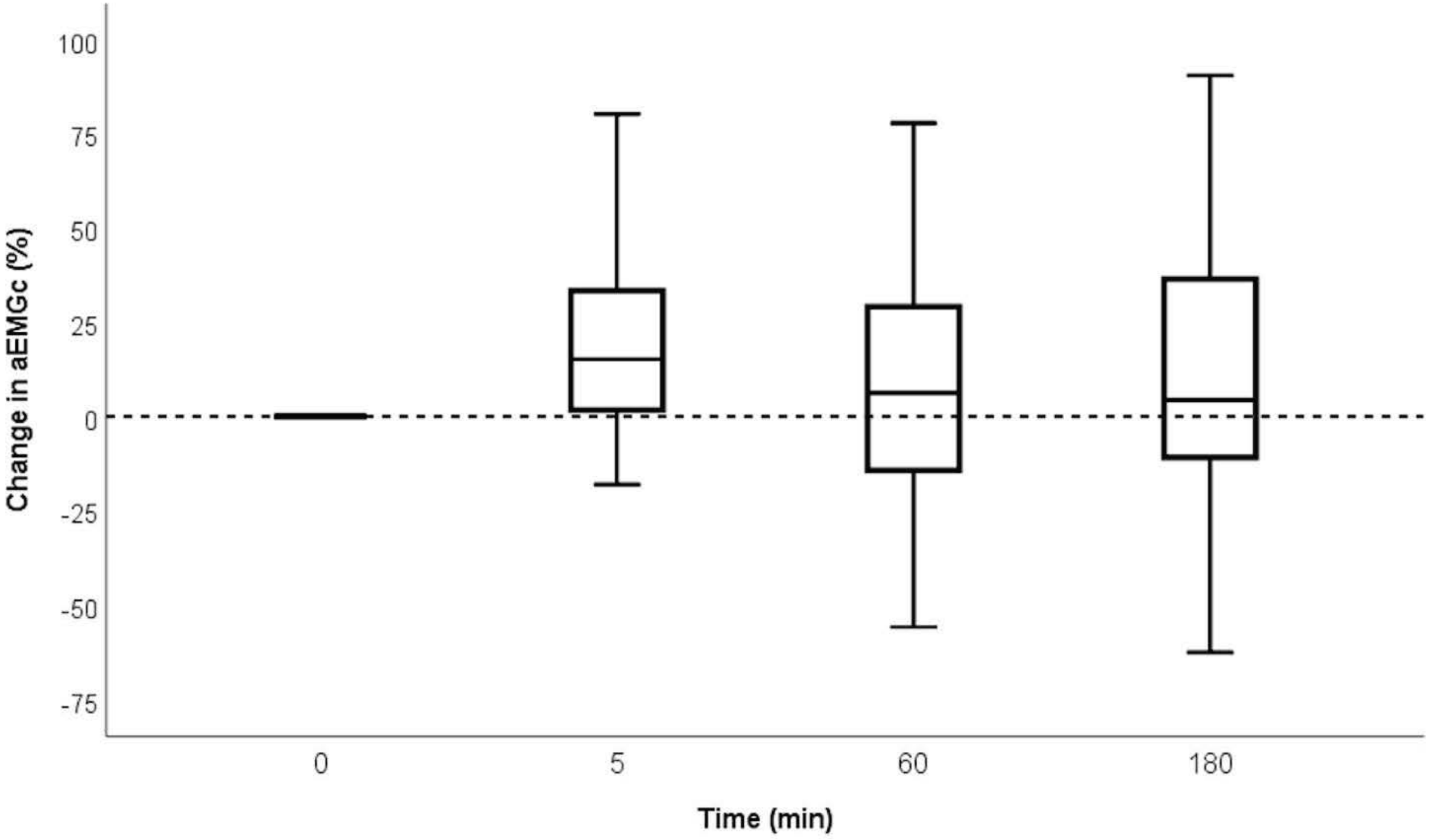


Figure 3. Boxplot of percentage change in area under the EMG curve over time
The ends of each box represent the upper and lower quartiles with the median being marked by a horizontal line inside the box. The whiskers are the two lines outside the box that extend to the highest and lowest observations.